

AMENDMENTS TO THE SPECIFICATION:

On page 1, after the title, please insert the following new paragraph as follows:

This application is a National Stage Application of PCT/JP2004/006384, filed May 12, 2004.

On page 24, please amend paragraph [0033] as follows:

(Dose)

The agent of the present invention contains an effective amount of at least one protease inhibitor, ~~and can be administered so that the protease inhibitor may be substantially retained at an effective concentration for a sufficient time to permit epithelialization in the site of adhesion formation.~~

Beginning on page 24, please amend paragraph [0034] as follows:

In the present invention, the acceptable amount and concentration of a protease inhibitor to administer can be determined within the range from the lowest concentration for achieving the effect, that is, “an effective amount”, to the highest concentration, “a pharmaceutically acceptable”, “a pharmacologically acceptable” concentration. A mixture of protease inhibitors can be administered intravenously or orally in a dosage form or medium (physiological saline) which is so suitable that the desired effect may be obtained in a cardiac site ~~(abdominal, thoracic, ophthalmic, cardiac, gynecologic tissue and the like) to prevent, inhibit or treat the adhesion formation.~~

On page 25, please amend paragraph [0035] as follows:

In the present invention, the term “effective amount” means a sufficient amount of the agent

for gaining a desired reaction with little or no toxicity to protect cardiac damage ~~prevent, inhibit or treat the adhesion formation~~. The precise required amount varies depending on an individual subject in species, age, body weight, general body conditions, or administration mode. A suitable "effective amount" can be also determined by the general prior art using the information ~~fact~~ provided herein and conventional methods.

Beginning on page 27, please amend paragraph [0042] as follows:

To elucidate the relationship between chymase activity and cardiac damage ~~adhesion formation~~, the effect of a representative serine protease inhibitor, the chymase inhibitor, Suc-Val-Pro-Phe^P(OPh)₂, was tested. This compound has been synthesized using a known methodology (Biochemistry, 30, p.485-493, 1991). More specifically, the reaction of Cbz-Val-OH (0.25 g, 1 mmol), DCC (0.2 g, 1 mmol) and the product of hydrogenolysis of Cbz-Val-Pro-Phe^P (OPh)₂ (0.584 g, 1 mmol) were dissolved in 30 ml of ethyl acetate and oil was added thereto. To this solution, 0.1 g (1 mmol) of succinic anhydride and 0.1 g of 5% Pd/C were added and the mixture was stirred under a hydrogen atmosphere until thin layer chromatography (TLC) showed only one new spot. The catalyst was removed by filtration and the organic layer was washed several times with water. After drying, the organic solvent was removed to give, for example, 0.45 g (65%) of a product as a hygroscopic solid (mp. 50-53°C: one spot on TLC, R_f=0.4; ³¹P NMR 19.75, 19.23 ppm, ratio 1:1, Anal. Calcd. for C₃₄H₄₀O₃N₃P.2H₂O: 59.56; H, 6.42. Found: C, 59.59; H, 6.42).

Beginning on page 32, please amend paragraph [0050] as follows:

(Experimental Example) Survival rate after the occurrence of myocardial infarction resulted by oral administration of Suc-Val-Pro-L-Phe^P(OPh)₂

The left coronary artery was ligated in Syrian hamsters (SLC, Co., Ltd., Shizuoka, Japan), 6 weeks of age, weighing 85 to 90 g, to prepare a myocardial infarction model (Jpn.J.Pharmacol., 86, p. 203-214 2001 life Sci. 71 p. 437-446 2002). Suc-Val-Pro-L-Phe^P(OPh)₂ (10 mg/kg) (nine cases) or a placebo (twenty three cases) has been forcibly orally administered using a sound once a day from the 3rd day before the model preparation to the 14th day after the model preparation, and the degree of myocardial infarction ~~adhesion~~ up to the 14th day following the model preparation was compared to study. It should be noted that the significant test was performed by log rank test using the survival curve.

As a result, the survival rate of the placebo group up to the 14th day was 39.1%, while that of the group in which Suc-Val-Pro-L-Phe^P(OPh)₂ (10 mg/kg) was administered from the day before the operation was 88.9%, indicating that the survival rate was significantly increased in the Suc-Val-Pro-L-Phe^P(OPh)₂ administration group (see Fig.1).

Similarly, the survival rate of the placebo group up to the 14th day was 39.1%, while that of the group in which Suc-Val-Pro-L-Phe^P(OPh)₂ (10 mg/kg) was administered orally from the day after the operation was 88.9%, indicating that the survival rate was significantly increased in the Suc-Val-Pro-L-Phe^P(OPh)₂ administration group (see Fig.2).

Suc-Val-Pro-L-Phe^P(OPh)₂ was administered before occurrence of myocardial infarction, allowing significant improvement of the survival rate, and further administered even after occurrence of myocardial infarction, allowing significant improvement. This indicates that Suc-Val-Pro-L-Phe^P(OPh)₂ is useful for preventing myocardial infarction and for improving the survival rate after myocardial infarction occurs.

[Industrial Applicability]

As described above, the agent for protecting cardiac damage of the present invention is

administered orally, allowing prevention of myocardial infarction and improvement of the survival rate even after the occurrence of myocardial infarction. Therefore, it is suggested that the agent is useful as an agent for protecting cardiac damage against arrhythmia, cardiac desmoplasia and heart-failure accompanying with myocardial infarction or the like.